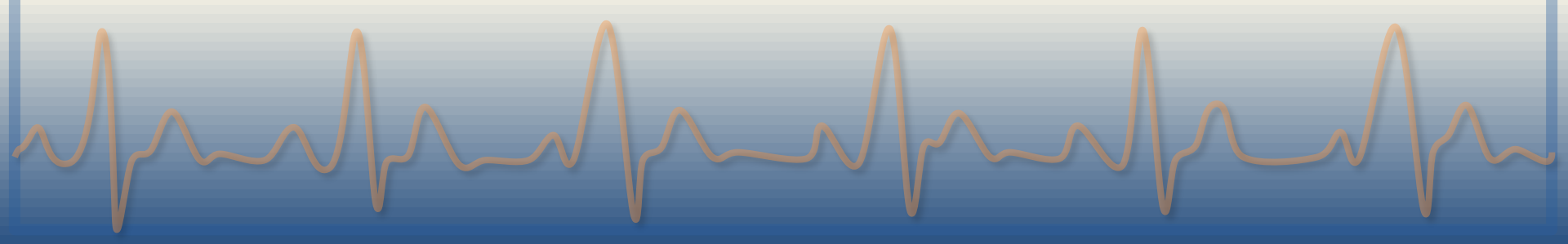
To CREST 2 or not to CREST 2:

That is the Question?

Gary S. Roubin MD PhD.
Chairman IMC. CREST 2 Trial.

Conflicts of Interest.

1. **Cook Inc.**
2. **Essential Medical Inc.**
3. **The Medicines Co.**



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American Heart Association

Asymptomatic Carotid Stenosis
J. David Spence

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CLINICIAN UPDATE

Strong and vocal opinions!

Strong

Asymptomatic Carotid Stenosis

J. David Spence, MD, FRCPC

Case Presentation: A 78-year-old woman, a retired primary school principal, was referred for a second opinion regarding a recommendation that she undergo stenting of a severe carotid stenosis. A bruit in the right carotid had led to a carotid ultrasound study and a diagnosis of 80% stenosis of the right internal carotid artery. This cognitive decline. Her serum lipids (in mg/dL) were total cholesterol 164, triglycerides 125, high-density lipoprotein 1.2, and low-density lipoprotein 2.56.

Her cardiologist told her that she was a walking time bomb and offered to stent her right internal carotid artery, but she subsequently read a column by Jane Brody in *The New York Times* on

Background

In the field of clinical pharmacology, it is not regarded as legitimate to compare drugs across studies; to compare the efficacy and safety of one treatment against another, therapies should be assessed in a double-blind, head-to-head comparison of one treatment versus the other. Many

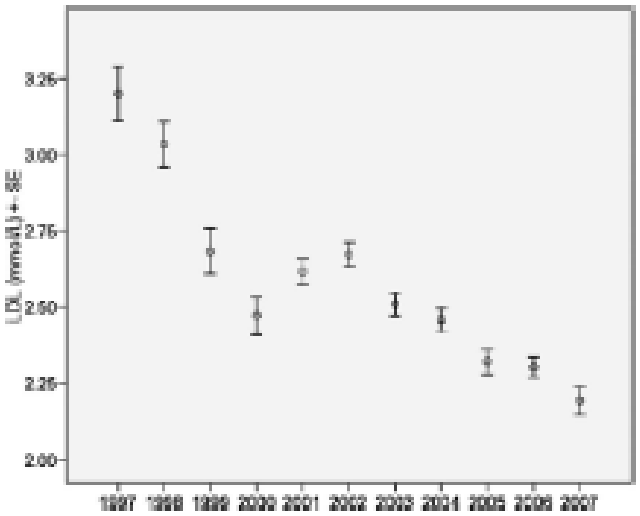

Figure 1. Decline in plasma levels of low-density lipoprotein (LDL) cholesterol at the time of referral to my vascular prevention clinics, by year, from 1997 to 2007. LDL cholesterol is shown in millimoles per liter; to convert to milligrams per deciliter, multiply by 38.67. The data are from 4378 patients referred to the Stroke Prevention Clinic or the Premature Atherosclerosis Clinic at University Hospital, London, Ontario, Canada. Reproduced from Spence et al.[4]

Supporting Evidence.

- Risk factors have declined with medical therapy.
- Populations of patients with atherosclerosis have had less stroke events.

conducted. A prospective population-based study in Oxfordshire, United Kingdom,[9] a clinic-based observational study in Canadian patients attending a stroke prevention clinic,[10] and a meta-analysis of published studies[11] have all shown that the risk of stroke in patients with asymptomatic carotid stenosis is now ≈0.5% per year. This is substantially lower than the risk of either stenting or endarterectomy in CREST. Objections from advocates of intervention that severity of stenosis was not taken into account in these studies were answered in a meta-analysis by Naylor.[12] In contrast to symptomatic carotid stenosis, in asymptomatic carotid stenosis, the severity of stenosis does not predict risk.[13] Therefore, the risks of stroke or death in CREST cannot legitimately be used to justify stenting or endarterectomy in unselected patients with asymptomatic carotid

and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. *Lancet*. 2004;363:1491–1502.

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Low Risk of Ipsilateral Stroke in Patients With Asymptomatic Carotid Stenosis on Best Medical Treatment

A Prospective, Population-Based Study

Lars Marquardt, MD; Olivia C. Geraghty, MRCP; Ziyah Mehta, PhD; Peter M. Rothwell, PhD

Background and Purpose—The annual risk of ischemic stroke distal to ≥50% asymptomatic carotid stenoses was ~2% to 3% in early cohort studies and subsequent randomized trials of endarterectomy. This risk might have fallen in recent years owing to improvements in medical treatment, but there are no published prognostic data from studies initiated within the last 10 years.

Methods—In a population-based study of all patients with transient ischemic attack (TIA) or stroke in the Oxford Vascular Study, we studied the risk of TIA and stroke in patients with ≥50% contralateral asymptomatic carotid stenoses recruited consecutively from 2002 to 2009 and given intensive contemporary medical treatment.

Results—Of 1153 consecutively imaged patients presenting with stroke or TIA, 101 (8.8%) had ≥50% asymptomatic carotid stenoses (mean age, 75 years; 39% women; 40% age ≥80 years). During 301 patient-years of follow-up (mean, 3 years), there were 6 ischemic events in the territory of an asymptomatic stenosis, 1 minor stroke (initially 50% to 69% stenosis), and 5 TIAs (2 initially 50% to 69% stenosis, 3 to 70% to 99% stenosis), 3 of which led to subsequent endarterectomy. The average annual event rates on medical treatment were 0.34% (95% CI, 0.01 to 1.87) for any ipsilateral ischemic stroke, 0% (95% CI, 0.00 to 0.99) for disabling ipsilateral stroke, and 1.78% (95% CI, 0.58 to 4.16) for ipsilateral TIA.

Conclusions—In the first study of the prognosis of ≥50% asymptomatic carotid stenosis to be initiated in the last 10 years, the risk of stroke on intensive contemporary medical treatment was low. Larger studies are required to determine whether this apparent improvement in prognosis is generalizable. (***Stroke*. 2010;41:e11-e17.**)

Key Words: carotid stenosis ■ stroke ■ TIA ■ statins

The neurology community believe that this is real.

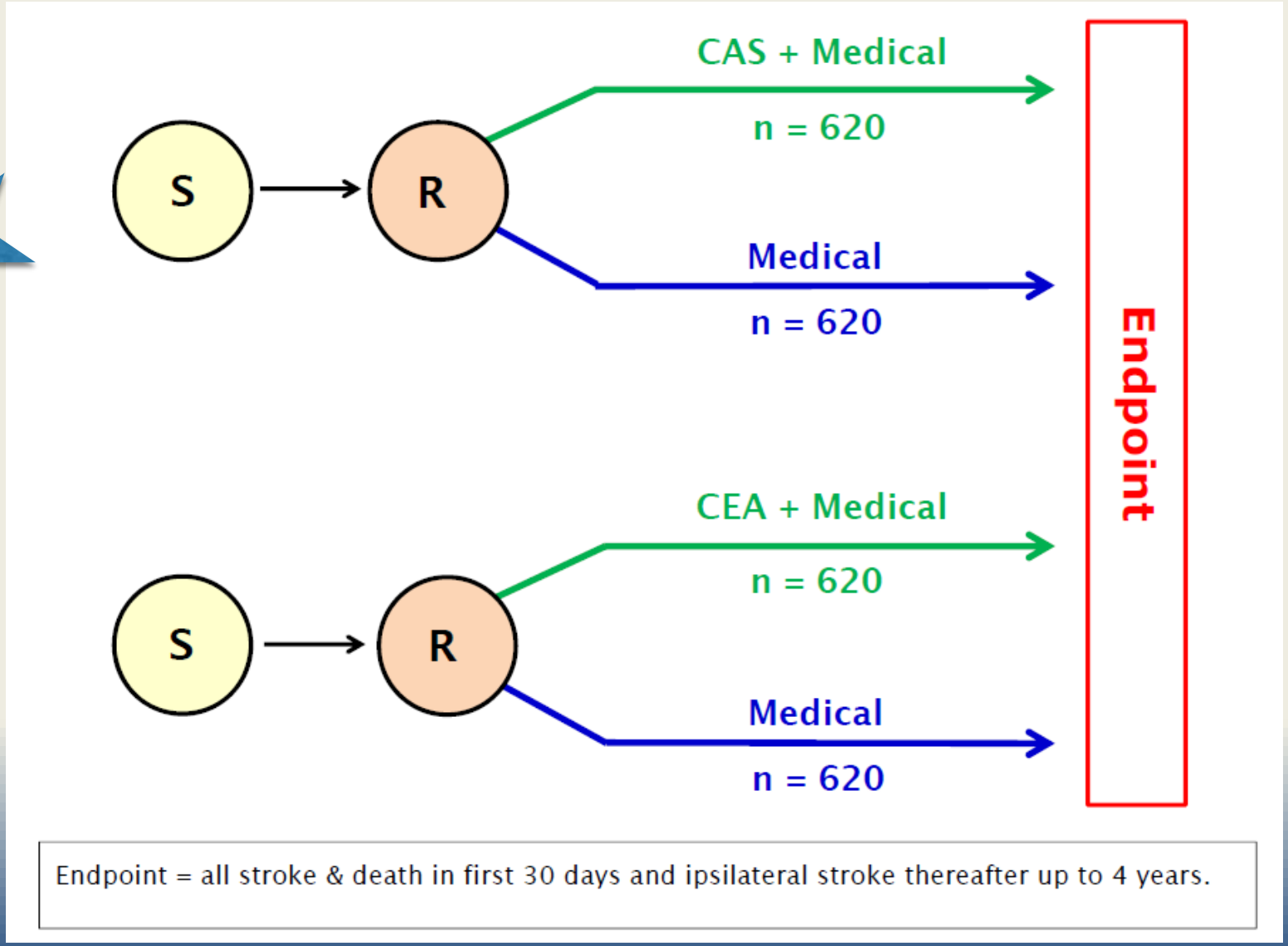
Optimal Medical Therapy prevents stroke?

They appreciate that OMT is the experimental therapy.

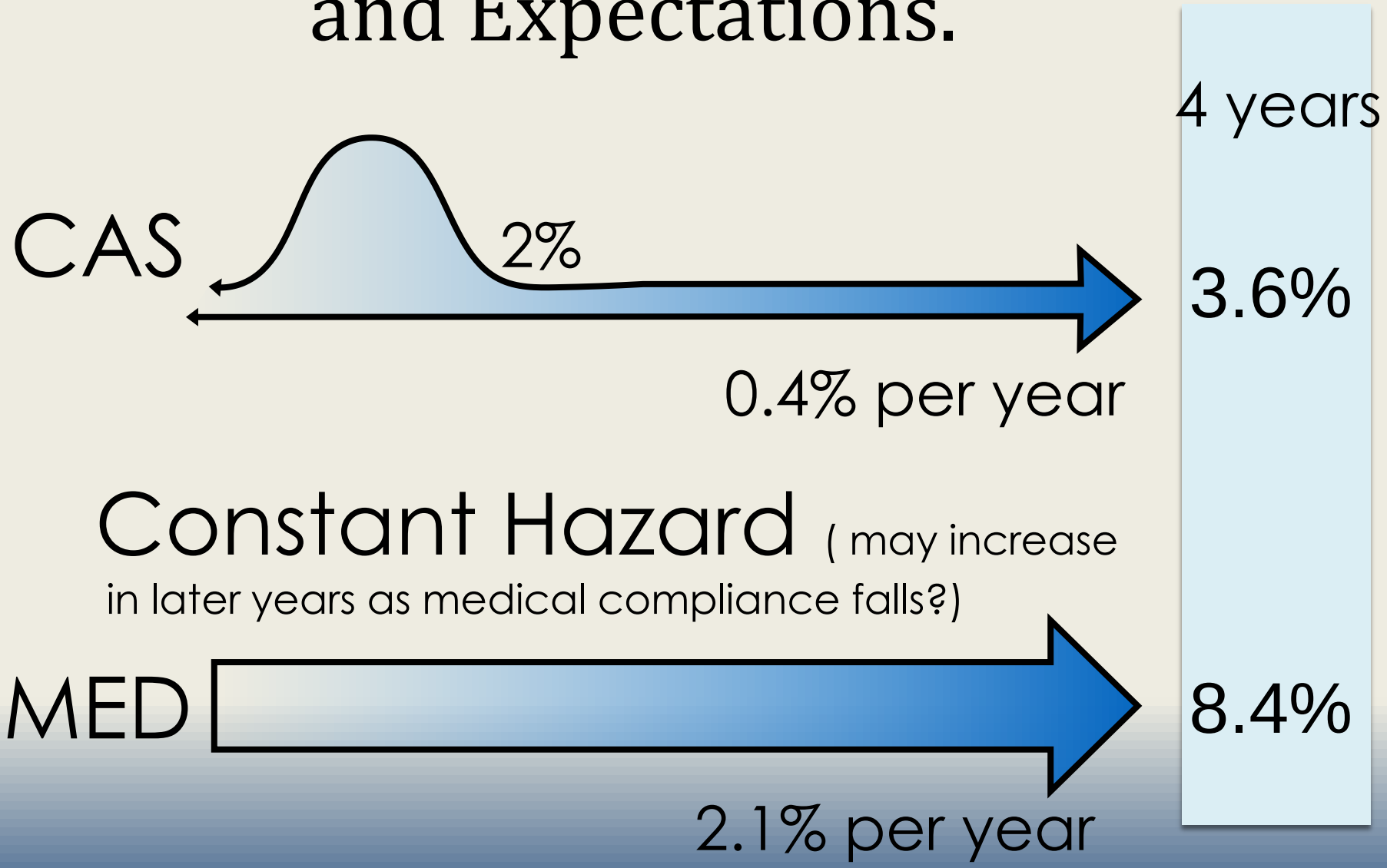
They are doing a trial to test the hypothesis that OMT is as good as revascularization.

We can stand by and criticize or participate to ensure that trial methodology provides fair comparison.

CREST-2 Parallel Study Design



Statistical Calculations and Expectations.



Trial Credibility

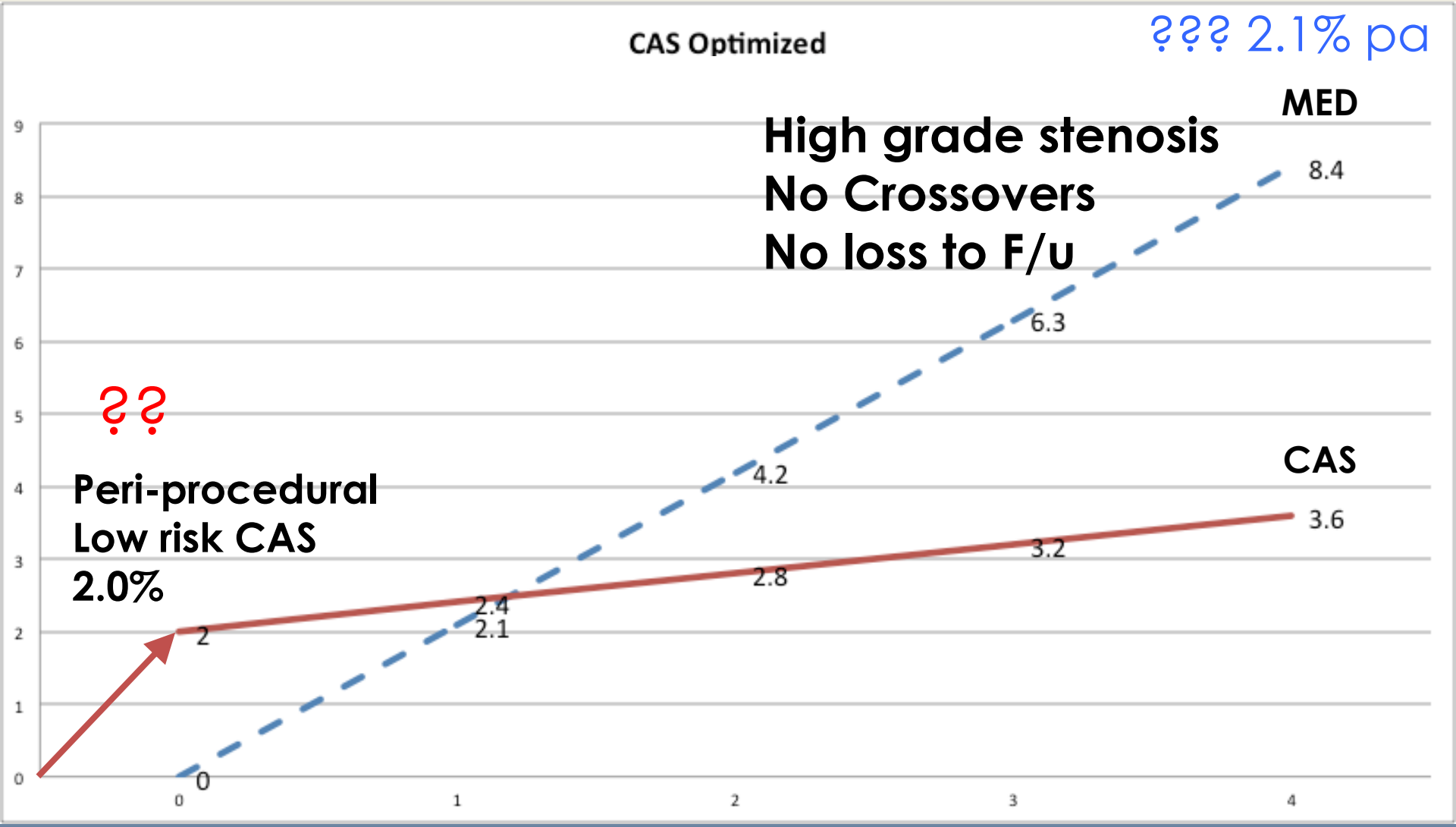
High Grade Stenosis ⇧ Events in the Medical Arm

- Young patients.
- Perfect 'Ideal' Anatomy

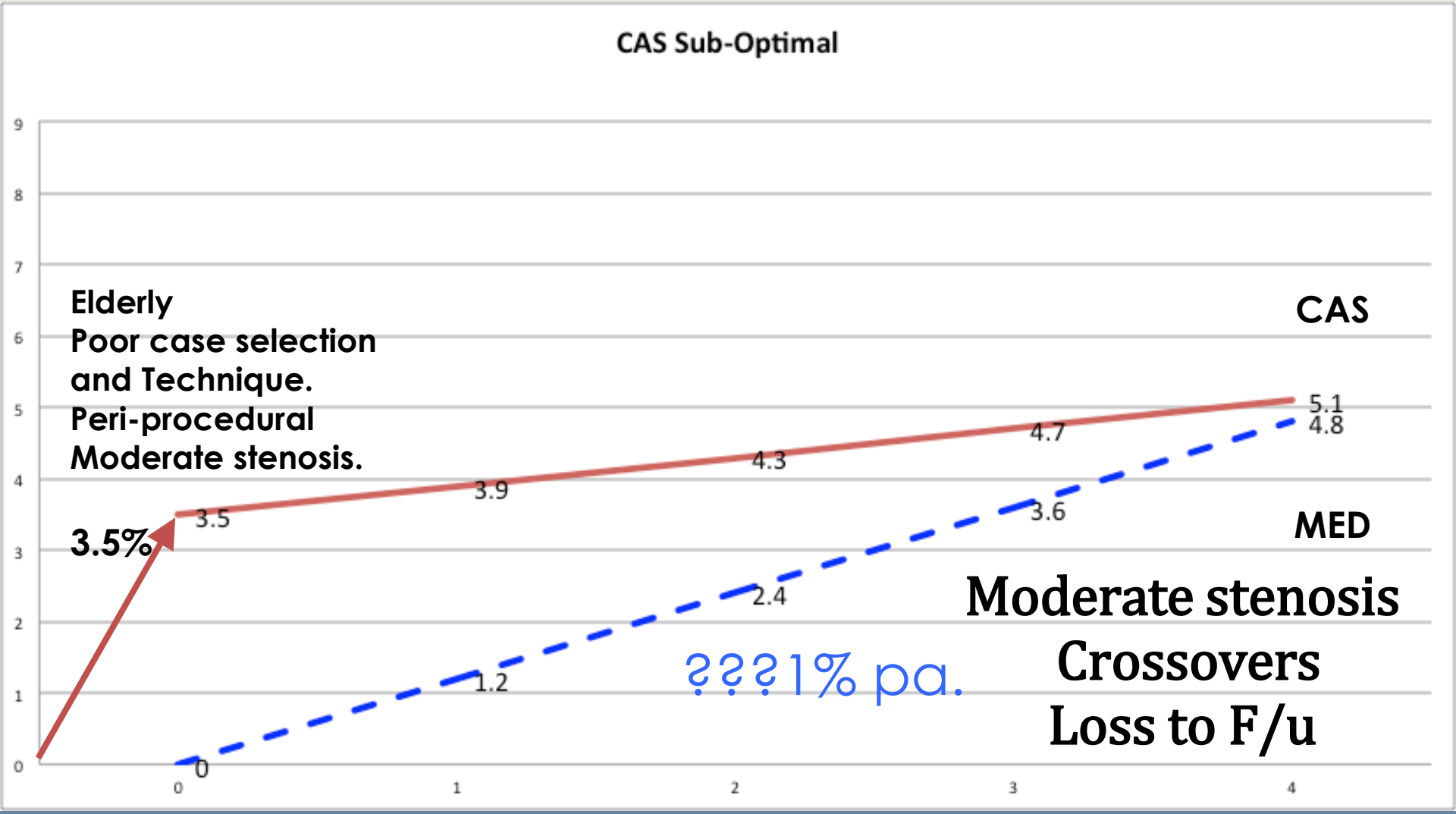
⇩ Events Stenting Arm

Skilled operators / Protocol driven optimal technique

Trial Credibility



What we do not want to see in CREST2
!Low Trial Credibility



Summary

1. **CREST2 is a reality. It is happening!**
2. **We can stand by and criticize or we can participate and contribute.**
3. **We must manage and control :**

Patient Selection in the stent arm.

Operator Credentialing.

Operations. (Crossovers).